

AVERY GOOKIN AND BRUCE ANTHONY PH.D., Department of Chemistry and Biochemistry, West Virginia Wesleyan College, Buckhannon, WV. 26201. Alcohol induced changes in E2F1/DP1 and Retinoblastoma binding in neural stem cells contributes to FASD phenotype.

Fetal Alcohol Spectrum Disorders (FASD) are a leading cause of neurodevelopmental disability. Children born with FASD suffer from a spectrum of, central nervous system damage, and characteristic abnormal facial features. Many of the phenotypic changes are associated with loss of cellular proliferation. Our previous studies suggest that changes in G1/S phase transition are responsible for this proliferative reduction and may well induce cell losses. Previous western and micro-array analysis demonstrated alcohol induced increases in expression of E2F1, DP-1, RB, Cyclin D1 and CDK4/6. Under normal growth conditions the transcriptional dimer E2F-1/DP-1 induces expression of many genes needed for proper DNA synthesis. This dimer is downregulated by binding of retinoblastoma (RB) to E2F1, and activation of S-Phase is marked by phosphorylation of Rb and subsequent release of E2F1. Although overexpression of several genes associated with proper G1/S phase progression suggest a mechanism for FASD loss of proliferation and cell numbers, it was important to confirm the functional significance of changes in protein levels. This set of experiments examined the changes in Rb/E2F1/DP1 protein-protein binding interactions and western analysis. We demonstrate alcohol induced changes in protein interactions between E2F1 and RB that help to define a mechanism for proliferative changes and induced cell losses associated with neuronal stem cells in FASD. By define the mechanism associated with many FASD phenotypes we can better address treatment strategies.